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|---|---|
| HUYNH, PHUONG N | |
| ART UNIT | PAPER NUMBER |
| 1644 | |

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/019,087 | FISCHER ET AL. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/19/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/03; 12/19/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-49 are pending and are being acted upon in this Office Action.

2. The disclosure is objected to because of the following informalities: (1) "Figures 37 through 55" on page 41, line 7 should have been "Figures 37 through 50" because there are only 50 figures in the specification as filed. (2) "09/591,642, filed June 9, 2000, and is a continuation of United States patent application 09/591,642, filed June 9, 2000" on page 1 lines 10-17 cannot be a continuation application of itself. Appropriate action is required.

3. Claim 36 is objected to because ", ,".

4. The International Preliminary Examination Report on PTO 1449 filed 1/21/03 has been considered but has been crossed out because said report is not appropriate on an issue patent. Further, the Downey et al reference (no. 26) and the Toh et al reference (no. 60) on PTO 1449 filed 12/19/01 have been crossed out because the journal title and date are missing.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for diagnosis of disseminated intravascular coagulation (DIC) comprising the steps of (a) adding a metal divalent ion and one or more clot inhibitor to a blood sample from a patient to cause the formation of a complex comprising C reactive protein and at least one human lipoproteins selected from the group consisting of VLDL, and IDL, while causing no fibrin polymerization, (b) measuring the formation of said complex overtime so as to derive a time-dependent measurement profile, (c) determining the slope of and /or total change in the time-dependent measurement profile, and (d) correlating the formation of the precipitate to the likelihood of mortality, the greater the formation of said complex, the greater the likelihood of death of the patient, **does not** reasonably provide enablement for any methods as set forth in claims 1-49. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for diagnosis of disseminated intravascular coagulation (DIC) comprising the steps of (a) adding calcium as one of the divalent metal ion and one or more clot inhibitor to a blood sample from a patient to cause the formation of a complex comprising C reactive protein and at least one human lipoproteins selected from the group consisting of VLDL, and IDL, while causing no fibrin polymerization, (b) measuring the formation of said complex overtime so as to derive a time-dependent measurement profile, (c) determining the slope of and /or total change in the time-dependent measurement profile, and (d) correlating the formation of the precipitate to the likelihood of mortality. The specification discloses only Calcium and thrombin inhibitor PPACK as the reagents for the claimed method. The addition of calcium causes the formation of a precipitate in the sample and the greater the complex formation (precipitate) between c reactive protein (CRP) and VLDL or IDL (Figure 42, page 38, line 35), the greater severity of the patient's hacmostatic dysfunction.

The specification does not teach how to make *any* one more "reagents" (claims 1, 18, 20, 32, 40 and 49), *any* inhibiting reagent (claim 32), *any* antibody capable of binding to *any* lipoprotein-acute phase protein binding site (claim 36) for a method of diagnosing *any* "condition" of the patient (Claim 1) or a method for testing the effectiveness of any therapeutic (claim 49). The term "reagent" or "inhibiting reagent" without the specific amino acid or chemical structure has no structure, much less function. Let alone predicting or correlating which "condition" of a patient associated with the formation of a complex (precipitate) over time comprising any lipoproteins and any acute phase protein, without causing any fibrin polymerization. There is insufficient guidance as to the structure of any "reagents", and any "inhibiting reagent". Given the indefinite number of reagents, there is insufficient working

example demonstrating all undisclosed reagent and/or inhibiting reagent are effective for causing formation of complex between any acute phase protein and any human lipoprotein, in turn, would be associated with a specific condition in a patient.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Given the indefinite number of undisclosed reagents, it is unpredictable which undisclosed one or more reagents would be useful for diagnose which condition in a patient.

With regard to antibody capable of binding to *any* lipoprotein-acute phase protein binding site, there is insufficient guidance as to which undisclosed lipoprotein the antibody binds, in turn, useful for diagnosis all condition in a patient. There is insufficient guidance as to the binding specificity of the antibody.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed antibody, it is unpredictable which undisclosed antibody is capable binding to which lipoprotein-acute phase protein binding site, in turn, would be useful for diagnosis of all condition such as impending death of a patient. Even if C reactive protein (CRP) forms complex with lipoprotein such as VLDL in the present calcium that could be measured over time, the formation of CRP-VLDL complex does not equate with impending death or mortality of all patient.

Row *et al* teach that acute phase protein such as C reactive protein forms complex with lipoprotein such as apoB, and VLDL in pathological condition such as atherosclerosis is calcium dependent and inhabitable by phophoryl choline (See abstract, in particular).

Li et al teach that lipoprotein such as amyloid P forms complex with HDL and VLDL but not with LDL (See abstract, in particular). Given the indefinite number of condition to be diagnosed, there is insufficient guidance as to which lipoprotein forming complex with which lipoprotein is associated with which condition, in addition to adding which undisclosed reagents to be added in the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 1-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* one more "reagents" (claims 1, 18, 20, 32, 40 and 49), *any* inhibiting reagent (claim 32), *any* antibody capable of binding to *any* lipoprotein-acute phase protein binding site (claim 36) for a method of diagnosing *any* "condition" of the patient (Claim 1) or a method for testing the effectiveness of any therapeutic (claim 49).

The specification discloses only a method for diagnosis of disseminated intravascular coagulation (DIC) comprising the steps of (a) adding calcium as one of the divalent metal ion and one or more clot inhibitor to a blood sample from a patient to cause the formation of a complex comprising C reactive protein and at least one human lipoproteins selected from the group consisting of VLDL, and IDL, while causing no fibrin polymerization, (b) measuring the formation of said complex overtime so as to derive a time-dependent measurement profile, (c) determining the slope of and /or total change in the time-dependent measurement profile, and (d) correlating the formation of the precipitate to the likelihood of mortality. The specification

discloses only Calcium and thrombin inhibitor PPACK as the reagents for the claimed method. The addition of calcium causes the formation of a precipitate in the sample and the greater the complex formation (precipitate) between c reactive protein (CRP) and VLDL or IDL (Figure 42, page 38, line 35), the greater severity of the patient's haemostatic dysfunction.

Other than the specific reagents calcium and thrombin inhibitor for a method of predicting an increased likelihood of system failure or mortality of a patient associated with disseminated intravascular coagulation, there is inadequate written description about the structure associated with function of any undisclosed "reagent" or "inhibiting reagent" without the specific amino acid or chemical structure, let alone predicting or diagnosing all condition such as increased the likelihood of mortality in patient.

With regard to antibody capable of binding to *any* lipoprotein-acute phase protein binding site, there is inadequate written about the binding specificity of the antibody, the structure of the immunogen, i.e., the binding site of which lipoprotein-acute phase protein without the specific amino acid sequence to which the antibody binds, in turn, the antibody is useful for diagnosis for all condition in patient. Given the indefinite number of undisclosed antibody binding to which undisclosed lipoprotein-acute phase protein, reagent, and/or inhibiting reagent, the claimed method for diagnosis of all condition such as impending death or mortality of a patient is not adequately described. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1-17, 19, 24 and 32-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The method in claims 1-17, and 32-48 is ambiguous and indefinite because it is not clear what method is being claimed.

The recitation of "said one or more reagents" in claims 19 and 24 has no antecedent basis in base claim 18 because the word "reagents" is not recited in claim 18.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 40-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Rowe *et al* (of record, Clin Exp Immunol 58(1): 237-44, Oct 1984; PTO 892).

Rowe *et al* teach a method comprising providing a test sample such as sera from patient with hyperlipoproteinaemias containing VLDL, adding a reagent such as Tris-saline-calcium which is a divalent metal cation to the sample (See page 241, first paragraph, in particular), and mixed with an acute phase protein such as human CRP (See page 241, first paragraph, in particular), measuring the formation of complex or precipitation by immunoelectrophoresis or gel electrophoresis, immunoprecipitation, and sucrose density gradient ultracentrifugation (See Figure 1, page 239, page 243, in particular) and correlating the formation of the reference complex to a concentration of lipoprotein (See Table 1, Fig 1, page 239, in particular). Rowe *et al* teach that CRP may contribute to pathophysiological processes, such as involving abnormalities of lipid deposition and distribution associated with atherosclerosis and fat embolism syndrome (See page 244, in particular). Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-7, 11, 13-16, and 32-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,169,786, of record, Dec 1992, PTO 892) in view of Rowe *et al.* (of record, Clin Exp. Immunol 58: 237-244, 1984; PTO 1449), and Canivet *et al.* (Acta Anaesthesiological Belgica 40(4): 263-268, 1989; PTO 1449).

The '786 patent teaches an assay that measure complex formation overtime such as APTT assay by determining the slope and/or total change in the complex over time to diagnosis a condition such as protein C deficiencies or deficiencies of clotting factors using activated partial thromboplastin time (APTT) assay. The reference method comprises adding one or more reagents such as a buffering reagent containing phospholipids, divalent metal cation such as calcium to initiate the clotting reaction (See column 2 line 30) and clot inhibitor such as heparin (column 5, line 11; Example 3 in particular) to a test sample such as plasma from a subject (See column 4, line 50, in particular), measuring the formation of complex over time by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time to derive (See column 5, line 15-30, in particular). The APTT assay is useful in monitoring abnormal clotting or clot or complex formation by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time. The clot signature (graph of turbidity over time) generated by an advanced instrument is useful in detecting certain disease states, including hypercoagulability for patients undergoing

heparin anticoagulant therapy (See entire document, column 3, line 14; column 5, line 8 to line 66, Fig. 5, in particular). The change in the clot signature and/or the rate of change (the change in reaction rate or velocity) is a useful tool to monitor the incidence of hemorrhagic complications in disseminated intravascular coagulation (DIC) which increase the mortality of patients (column 5, line 21-30; column 7 line 37-53; column 8, example 7, in particular).

The claimed invention differs from the teachings of the reference only that the method monitoring the acute phase protein and lipoprotein complex instead of clotting factors forming complex with protein C by measuring the formation of complex overtime.

Rowe *et al.* teach acute phase protein such as human C-reactive protein (CRP) can form complex with lipoprotein such as VLDL, LDL, apolipoprotein B (ApoB), chylomicrons in a calcium dependent manner without the fibrin polymerization (See entire document, page 237 in particular) and the acute phase protein and lipoprotein interaction can block by inhibitor such as phosphorylcholine, and EDTA (page 239-241). Rowe *et al* teach that CRP may contribute to pathophysiological processes, such as involving abnormalities of lipid deposition and distribution associated with atherosclerosis and fat embolism syndrome (See page 244, in particular).

Canivet *et al* teach that there is a positive correlation between serum levels of HDL, cholesterol, phospholipid, ApoB and C-reactive protein after surgery, myocardial infraction, trauma and burn injury and measuring the changes in lipid profile and serum levels of CRP following surgery are of value in assessment of the host responses to critical illness (See entire document, Page 263, 266-267 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as CRP and lipoprotein such as VLDL as taught by Rowe using the assay that measured complex formation over time as taught by the '786 patent.

One having ordinary skill in the art would have been motivated to measure the acute phase protein-lipoprotein complex in view of the teachings of the secondary reference because Rowe *et al.* teach that the CRP-VLDL complex may be important for the role of CRP in health and disease such as atherosclerosis (See abstract, in particular). Canivet et al teach that there is a positive correlation between serum levels of HDL, cholesterol, phospholipid, ApoB and C-reactive protein after surgery, myocardial infraction, trauma and burn injury and measuring the changes in lipid profile and serum levels of CRP following surgery are of value in assessment of the host responses to critical illness (See entire document, Page 263, 266-267 in particular). The

'786 patent teaches that change in the clot signature and/or the rate of change (the change in reaction rate or velocity) is a useful tool to monitor the incidence of hemorrhagic complications in disseminated intravascular coagulation (DIC) which increase the mortality of patients (column 5, line 21-30; column 7 line 37-53; column 8, example 7, in particular).

Applicants' arguments filed 12/19/01 have been fully considered but are not found persuasive.

Applicants' position is that (1) there is no motivation or evidence from the prior art to combine these components for combination in the manner claimed. (2) Claim 1 recites "while causing substantially no fibrin polymerization" concerning monitoring the precoagulation phase of an APTT-like waveform. The procedure of Carroll (the '786 patent) requires observation of clot formation. The procedure of Carroll (the '786 patent) would be rendered inoperative if modified to carry out the present invention without knowledge of the claimed invention. Nothing in the remaining references cures this inoperability. (3) There is no motivation to combine the references since Carroll concerns a blood coagulation assay and Rowe concerns protein/lipoprotein assay. (4) None of the references in combination or alone teaches the step (d) of claim 32 or step (d) of claim 40.

However, claim 1 does not recite "monitoring the precoagulation phase of an APTT-like waveform". Further, claim 1 does not recite the specific condition that the claimed method can be used to diagnose. The detection of other immune complex such as C-reactive protein forming complex with lipoprotein VLDL does not involved fibrin polymerization as taught by Rowe et al (See entire document). The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied , 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done " (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. The strongest rationale for combining references is recognition in the art that some advantage or

expected beneficial result would have been produced by their combination. In instant case, Rowe *et al.* teach acute phase protein such as human C-reactive protein (CRP) can form complex with lipoprotein such as VLDL, LDL, apolipoprotein B (ApoB), chylomicrons in a calcium dependent manner without the fibrin polymerization (See entire document, page 237 in particular); the formation of CRP-VLDL complex is associated with lipid deposition, atherosclerosis and fat embolism syndrome (See page 244, in particular). The '786 patent teaches an assay that measure complex formation overtime such as APTT assay by determining a slope and/or total change in the complex over time to diagnosis complex formation in condition such as clotting in a patient. The APTT assay is useful in monitoring abnormal clotting or complex formation by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as CRP and lipoprotein such as VLDL as taught by Rowe using the assay that measured complex formation over time as taught by the '786 patent. One having ordinary skill in the art would have been motivated to measure the acute phase protein-lipoprotein complex in view of the teachings of the secondary reference because Rowe *et al.* teach that the CRP-VLDL complex may be important for the role of CRP in health and disease such as atherosclerosis (See abstract, in particular). Canivet et al teach that there is a positive correlation between serum levels of HDL, cholesterol, phospholipid, ApoB and C-reactive protein after surgery, myocardial infraction, trauma and burn injury and measuring the changes in lipid profile and serum levels of CRP following surgery are of value in assessment of the host responses to critical illness (See entire document, Page 263, 266-267 in particular). The '786 patent teaches that change in the clot signature and/or the rate of change (the change in reaction rate or velocity) is a useful tool to monitor the incidence of hemorrhagic complications in disseminated intravascular coagulation (DIC) which increase the mortality of patients (column 5, line 21-30; column 7 line 37-53; column 8, example 7, in particular). The recitation of the extend of inhibition of complex formation is within the purview of one ordinary skill in the art at the time of the invention since the '786 patent teaches that the clot formation (complex formation) overtime is useful monitoring and testing the effectiveness of any therapeutic such as heparin in heparin therapy or extrinsic clotting factors by measuring the complex formation over time (See column 5, lines 56-58, in particular).

15. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over as being unpatentable over US Pat No 5,169,786, of record, Dec 1992, PTO 892) in view of Rowe *et al.* (Clin Exp. Immunol 58: 237-244, 1984; PTO 1449), and Canivet *et al.* (Acta Anaesthesiological Belgica 40(4): 263-268, 1989; PTO 1449) as applied to claims 1-7, 11, 13-16, and 32-39 and further in view of Li *et al* (Biochem & Biophys Res Comm 244: 249-252, 1998; PTO 892).

The combined teachings of the '786 patent, Rowe et al and Canivet et al have been discussed.

The claimed invention in claim 11 differs from the combined teachings of the references only that the method wherein the acute phase protein is SAA.

Li *et al* teach acute phase protein such as serum amyloid protein forms complex with High Density Lipoprotein (HDL) as well as Very Low Density Lipoprotein (VLDL) but not with Low Density Lipoprotein (LDL) and the complex formation depends on calcium (see abstract, page 251, column 1, in particular). Li *et al* teach that the complex or aggregation closely relates to the concentration of SAP (See page 251, column 2, in particular). Li *et al* teach that SAA and lipoproteins are present in all types of amyloid deposits, including Alzheimer's disease, and atherosclerotic lesions (See page 251, column 2, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as SAP and lipoprotein such as VLDL and HDL as taught by Li et al using the assay that measured complex formation over time as taught by the '786 patent.

One having ordinary skill in the art would have been motivated to measure the acute phase protein-lipoprotein complex such as SAA-VLDL as taught by the Li et al and/or CRP-VLDL as taught by Row et al using the assay as taught by the '786 patent because Li *et al* teach that SAA and lipoproteins are present in all types of amyloid deposits, including Alzheimer's disease, and atherosclerotic lesions (See page 251, column 2, last paragraph, in particular). Rowe *et al* teach that CRP may contribute to pathophysiological processes, such as involving abnormalities of lipid deposition and distribution associated with atherosclerosis and fat embolism syndrome (See page 244, in particular). The '786 patent teaches monitoring complex formation by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time and the clot signature (graph of turbidity over time) generated by an advanced instrument is useful in detecting certain disease states such as

hypercoagulability for patients undergoing heparin anticoagulant therapy (See entire document, column 3, line 14; column 5, line 8 to line 66, Fig. 5, in particular).

16. Claims 40-41, and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowe *et al* (of record, Clin Exp Immunol 58(1): 237-44, Oct 1984; PTO 892) in view of US Pat No 5,169,786, of record, Dec 1992, PTO 892).

The teachings of Rowe et al have been discussed supra. Rowe et al further teach that the complex formation is between VLDL and acute phase protein such as C-reactive protein. Rowe *et al* teach that CRP may contribute to pathophysiological processes, such as involving abnormalities of lipid deposition and distribution associated with atherosclerosis and fat embolism syndrome (See page 244, in particular).

The claimed invention in claim 44 differs from the teachings of the reference only that the method wherein the formation of the complex and the formation of the additional complex are measured over time so as to provide respective first and second time-dependent measurement profiles.

The claimed invention in claim 45 differs from the teachings of the reference only that the method wherein the measured additional complex and the measured initial complex together are correlated to a total amount of acute phase protein in the test sample.

The claimed invention in claim 46 differs from the teachings of the reference only that the method wherein the acute phase protein is C-reactive protein.

The '786 patent teaches an assay that measure complex formation overtime such as APTT assay by determining the slope and/or total change in the complex over time to diagnosis a condition such as protein C deficiencies or deficiencies of clotting factors using activated partial thromboplastin time (APTT) assay. The reference method comprises adding one or more reagents such as a buffering reagent containing phospholipids, divalent metal cation such as calcium to initiate the clotting reaction (See column 2 line 30) and clot inhibitor such as heparin (column 5, line 11; Example 3 in particular) to a test sample such as plasma from a subject (See column 4, line 50, in particular), measuring the formation of complex over time by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time to derive (See column 5, line 15-30, in particular). The APTT assay is useful in monitoring abnormal clotting or clot or complex formation by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution

over time. The clot signature (graph of turbidity over time) generated by an advanced instrument is useful in detecting certain disease states, including hypercoagulability for patients undergoing heparin anticoagulant therapy (See entire document, column 3, line 14; column 5, line 8 to line 66, Fig. 5, in particular). The change in the clot signature and/or the rate of change (the change in reaction rate or velocity) is a useful tool to monitor the incidence of hemorrhagic complications in disseminated intravascular coagulation (DIC) which increase the mortality of patients (column 5, line 21-30; column 7 line 37-53; column 8, example 7, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as CRP and lipoprotein such as VLDL as taught by Rowe using the assay that measure the formation of complex (precipitation) over time as taught by the '786 patent.

One having ordinary skill in the art would have been motivated to because monitoring abnormal complex formation by measuring the turbidity (decrease optical transmittance or absorbance as a result of precipitate formation) of the solution over time and the graph of turbidity over time) generated by an advanced instrument is useful in detecting certain disease states, including hypercoagulability for patients undergoing heparin anticoagulant therapy (See entire document, column 3, line 14; column 5, line 8 to line 66, Fig. 5, in particular). The change in the turbidity over time and/or the rate of change (the change in reaction rate or velocity) is/are useful tool to monitor complications in disease such as disseminated intravascular coagulation (DIC) that increases the mortality of patients (column 5, line 21-30; column 7 line 37-53; column 8, example 7, in particular). It is within the purview of one ordinary skill in the medicinal art to measure complex formation more than once over time to monitor complex formation among various coagulation factors as taught by the '786 patent (See column 1, lines 31, in particular).

17. The method for diagnosis of disseminated intravascular coagulation (DIC) comprising the steps of (a) adding calcium as one of the divalent metal ion and one or more clot inhibitor to a blood sample from a patient to cause the formation of a complex comprising C reactive protein and at least one human lipoproteins selected from the group consisting of VLDL, and IDL, while causing no fibrin polymerization, (b) measuring the formation of said complex overtime so as to derive a time-dependent measurement profile, (c) determining the slope of and /or total change in the time-dependent measurement profile, and (d) correlating the formation of the precipitate to the likelihood of mortality and the method for testing the effectiveness of a therapeutic for

disseminated intravascular coagulation (DIC) by monitoring the formation of a complex comprising C reactive protein and at least one human lipoproteins selected from the group consisting of VLDL, and IDL are free of prior art.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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